

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 7

REMARKS/ARGUMENTS

Claims 1-24 are pending in the instant application. Claim 8 and 10-24 have been withdrawn from consideration and subsequently canceled by Applicants in this response. Claims 1-7 and 9 have been rejected. Claims 1 and 9 have been amended. Reconsideration is respectfully requested in light of the following remarks.

I. Finality of Restriction Requirement

The Examiner has made final the Restriction Requirement mailed November 12, 2002. Therefore, in an earnest effort to advance the prosecution of this case, Applicants have canceled nonelected claims 8 and 10-24, without prejudice. In light of the finality of this Restriction Requirement, Applicants reserve the right to file a divisional application to the canceled subject matter.

II. Amendment of title

The Examiner suggests that the title is not descriptive and has required a new title indicative of the invention in which the claims are directed. Therefore, in an earnest effort to advance the prosecution of this case and in accordance with the Examiner's suggestion, Applicants have

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 8

amended the title to be descriptive of the invention to which the claims are directed. Specifically, the title has been amended to "METHODS FOR THE TREATMENT OF A CONDITION REMEDIABLE BY ADMINISTRATION OF A SELECTIVE ANDROGEN RECEPTOR MODULATOR".

III. Information Disclosure Statement

The Examiner suggests that the Information Disclosure Statements filed 10/15/01, 8/23/02 and 10/11/02 failed to comply with the provisions of 37 C.F.R. 1.97, 1.98 and MPEP 609.

Specifically, the Examiner suggests that the 10/15/01 IDS failed to comply because references AA and AB were never published. It is respectfully pointed out, however, that these are pending U.S. patent applications. They have been identified in the Information Disclosure Statement in accordance with the requirements of 37 C.F.R. 1.98 by the inventor, application number and filing date. Further, the instant application claims priority to the provisional applications from which references AA and AB claim priority. Thus, in accordance with 1.98(d) Applicants do not believe that copies of such applications need be provided.

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 9

However, in an earnest effort to facilitate the prosecution of this case, Applicants are providing herewith copies of these pending U.S. Applications. Since Applicants' IDS submitted 10/15/01 clearly constituted a bona fide attempt to comply with 37 C.F.R. 1.98, it is respectfully requested that these applications be considered and entered into the record of this case.

Applicants are also submitting herewith a Supplemental IDS and the requisite fee citing U.S. Patent Application Serial No. 10/322,306 and 10/322,077. These are continuation-in-part applications of U.S. Patent Application Serial No. 09/885,798 and 09/885,381, respectively, which were cited in the IDS submitted October 15, 2001 by Applicants.

The Examiner also suggests that the 8/23/02 IDS failed to comply because references BM, BN, BP, CF-CI, CV-CX, FS-FU, and FW-FX are in a foreign language and references JA-JB, KA-KB, KO-KP and KR-KS do not have a listed publication date.

It is respectfully pointed out, however, that English Abstracts summarizing the teachings of each of references BM, BN, BP, CF, CH, CI, CW, CX, FS, FT, FU and FX and, thus, a concise explanation of their relevance with respect to the instant invention were provided with the 8/23/02 IDS, thus

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 10

meeting the requirements of 37 C.F.R. 1.98 3(i). With respect to references CG and FW, English Abstracts indicative of their relevance with respect to the instant invention are being provided herewith. With respect to reference CV, it is respectfully pointed out that the corresponding European application EP277476 was also provided as reference CE in English. Consideration of these references is therefore also respectfully requested.

With respect to publication dates for references JA and JB, these are clearly indicated on the Chemical Abstracts submitted with the IDS as 1959 and 1966, respectively.

With respect to references KA, KB, KO, KP, KR and KS, these are copies of results from searches performed by Applicants. Copies of those references identified from these searches, which were separately then ordered and obtained by applicants were also provided in the IDS. For example, U.S. Patent 3,261,845, identified in search KA is provided as reference FO of the IDS. WO 2000/06525, WO 98/16830, U.S. Patent 3,998,833, U.S. Patent 3,821,232, U.S. Patent 3,965,264, U.S. Patent 4,089,650, U.S. Patent 3,923,490, U.S. Patent 3,997,293, Chen et al. 1999, Kirby et al. 1985, Tosunyan et al. 1992, Krow et al. 1982, and U.S. Patent

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 11

4,892,578 identified in search KB are provided as references EE, DQ, BG, BC, BE, BH, BD, BF, HQ, HT, HS, HV, and CS, respectively. Wijnberg et al. 1982, Grogan et al. 1963, Bockstahler et al. 1968, Joshi et al. 1983, Gringauz et al. 1968, U.S. Patent 3,261,845, Dominianni et al., Chem Abstr. 57, Jolivet 1960, Maruyama et al. 1981, U.S. Patent 3,343,940, Kwart et al. 1952, Berson et al. 1954, and Mel'nikow et al. 1956 identified in search KO are provided as references IK, IL, IE, IG, IM, FO, JN, IP, IQ, IR, BA, IT, IU, and IY or IZ, respectively. U.S. Patent 3,261,845 identified in search KP is provided as reference FO. GB 1039020 identified in search KR is provided as reference GA. JP 7-144477, CN 1050877, DE 2365677, U.S. Patent 3,906,102, and U.S. Patent 3,925,554 identified in search KS are provided as references FX, FY, FZ, FP, and FO respectively. Applicants provided these search results in an earnest effort to provide the Examiner with the opportunity to consider the same information that was considered by the Applicants. See MPEP 609. However, should the Examiner maintain that the search results of KA, KB, KO, KP, KR and KS will not be considered, Applicants have still clearly met their duty of disclosure since references identified therein, which were obtained by Applicants based on

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 12

these search results, were also provided with the IDS.

IV. Rejection of Claims 1-7 and 9 under 35 U.S.C. 112, first paragraph

Claims 1-7 and 9 have been rejected under 35 U.S.C. 112, first paragraph. The Examiner has acknowledged the specification to be enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD). However, the Examiner suggests that the specification does not reasonably provide enablement for a method of inhibiting the growth of hormone dependent tumor cells by administering any selective androgen receptor modulator that interacts with any androgen receptor complex.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's characterization of the claimed invention. Contrary to the Examiner's suggestion, claims of the instant application are not drawn to administering any selective androgen receptor modulator that interacts with any androgen receptor complex, but rather are drawn to administering a selective androgen receptor modulator which exhibits antagonist activity in a hormone-dependent tumor while

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 13

exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor. In accordance with MPEP 2164, it is this claimed invention that one skilled in the art must be enabled to make and use for the application to meet the enablement requirements of 35 U.S.C. 112, first paragraph.

Multiple methods, in addition to that acknowledged by the Examiner to be enabling for the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain, (AR-LBD) are set forth in the specification to make and/or identify selective androgen receptor modulators (SARMS) for use in the present invention which exhibit antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor.

The Examiner is respectfully directed to page 8, line 13 to page 9, line 5 of the instant specification wherein methods are taught for ascertaining antagonist activity in hormone-dependent tumors via screening for inhibition of growth *in vitro* in hormone-dependent tumor cell lines. As taught in the specification and evidenced by the multiple references cited at this section of the application, screening in these cell

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 14

lines is well accepted by those skilled in the art as indicative of the pharmacology of human hormone-dependent tumors. The Examiner is also respectfully directed to page 9, lines 6-21 of the specification wherein methods are taught for ascertaining no activity or agonist activity *in vitro* in normal nontumor cell lines. Also, see page 9, line 22 through page 10, line 20 of the specification wherein *in vivo* models widely recognized as having a direct correlation to the effects of the agents on the AR Pathways are taught for identifying SARMs for use in the claimed methods.

Additional details regarding use of these *in vitro* and *in vivo* models are set forth in the Examples 3 through 13 at pages 85-98 of the instant specification.

The Examiner is further directed to page 21 of the specification beginning at line 5 wherein preferred SARMs for use in the claimed methods of the present invention are defined by their activity in these *in vitro* and *in vivo* models.

Further, as taught beginning at page 44 page, line 2 of the instant specification, it was these *in vitro* and *in vivo* assays that were used by Applicants to identify exemplary

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 15

SARMs set forth in the application and used in the claimed methods.

Clearly, the specification is enabling for alternative methods, in addition to the method relating to the atomic structural coordinate listing (Table A) of an androgen receptor-ligand binding domain (AR-LBD), to make/identify SARMs which exhibit antagonist activity in a hormone-dependent tumor while exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor and to use such SARMs in the claimed invention.

Accordingly, withdrawal of this rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

Claim 9 is further rejected under 35 U.S.C. 112, first paragraph, because the Examiner suggests that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. The Examiner has acknowledged the specification to be enabling for SARM compounds that were tested *in vitro* and *in vivo* to determine whether treatment was effective in remedying a condition in prostate tumors and various cell lines as seen in the Examples. However, the Examiner suggests that the

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 16

specification does not reasonably provide enablement for a method of treatment of all conditions listed in claim 9 by administering a selective androgen receptor modulator in an effective way.

Applicants respectfully disagree.

The test of enablement, as set forth in MPEP 2164.01, is whether one reasonably skilled in the art could make and use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. In accordance with MPEP 2164.01(c), when one skilled in the art, based on knowledge of compounds having similar physiological or biological activity can discern an appropriate method of use without undue experimentation, this is sufficient to satisfy 35 U.S.C. 112, first paragraph.

In the instant application, Applicants have demonstrated through multiple *in vitro* and *in vivo* experiments the ability of exemplary SARMs of the present invention to bind to the androgen receptor and inhibit or antagonize its function in hormone-dependent tumors while exhibiting agonist activity against other, nontumor tissues containing the androgen receptor. See in particular page 44-46 of the instant specification and Examples 3-13. Such evidence of

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 17

pharmacological activity is clearly supportive of the use of these SARMS in additional known androgen-receptor mediated disorders as set forth in claim 9, particularly since modulation of androgen receptor function is an established therapeutic strategy for treatment of such conditions.

Thus, one skilled in the art could make and use the invention as set forth in claim 9 without undue experimentation.

Therefore, the instant specification meets the enablement requirements of 35 U.S.C. 112, first paragraph, with respect to claim 9 and withdrawal of this rejection is respectfully requested.

V. Rejection of Claims 1-7 and 9 under 35 U.S.C. 112, second paragraph

Claims 1-7 and 9 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

In particular, claim 1 is suggested to be vague and indefinite because, in line 4, the phrase "exhibits antagonist activity" does not include sufficient antecedent basis as to

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 18

what the antagonist activity is directed against.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to clarify that the antagonistic activity is directed against growth of the hormone-dependent tumor. Support for this amendment can be found throughout the specification, for example, at page 4, lines 5-7, page 7, lines 17-20 and page 8, lines 16-18.

Claim 9 is also rejected as vague and indefinite due to its reference to a non-elected claim. Accordingly, in an earnest effort to advance the prosecution of this case, claim 9 has been amended to be independent. Support for the amendment to claim 9 is provided in claim 8, now canceled.

Claim 9 has also been amended to provide the full name of VEGF as vascular endothelial growth factor in accordance with the Examiner's suggestion and the well known use of this abbreviation.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph, is respectfully requested in light of these amendments which make explicit what was implicit in the original claims.

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 19

VI. Rejection of Claims 1-7 and 9 under 35 U.S.C. 103

Claims 1-7 and 9 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe et al. (U.S. Patent 6,004,554) in view of Zhi et al. (U.S. Patent 6,358,947) and Li et al. (U.S. Patent 6,469,024). The Examiner suggests that it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the administration of selective androgen receptor modulators (as stated by Zhi et al. and Li et al.) in the methods of inhibiting and treating prostate tumor cells (as stated by Thorpe et al) with a reasonable expectation of success. The Examiner suggests that motivation to do so is given by Thorpe et al. who teach that developing successful antitumor agents via selective target agents and the teaching of Zhi et al. and Li et al. relating to compounds that target androgen receptors.

Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully disagree with the Examiner's characterization of the Zhi et al. and Li et al. patents as teaching selective androgen receptor modulators. Both the specification and claims of the instant application

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 20

clearly require a SARM for use in the present invention to exhibit antagonist activity in hormone-dependent tumors while exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor. Neither Zhi et al. nor Li et al. teach such compounds.

Zhi et al. describe nonsteroidal compounds that are primarily high affinity, highly selective modulators of progesterone receptors, not androgen receptors. While there is mention that these compounds may modulate a process mediated by an androgen receptor (see claim 4), it is clear from teachings at column 4, lines 35-48, of this patent, that such activity is secondary to its progesterone receptor modulating ability. Accordingly, the compounds of Zhi et al. are clearly not SARMS as defined in both the detailed description and claims of the instant application.

Li et al. describe tetrahydroisoquinoline analogs for stimulating endogenous production and/or release of growth hormone. While Li et al. teach at column 44, lines 47-61 that their analogs may be administered in combination with a selective androgen receptor modulator such as taught by Edwards, J.P. et al. Bio Med. Chem Let. 9, 1003-1008 (1999) and Hamann, L.G. et al. J. Med. Chem. 42:210-212 (1999), the

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 21

analogues taught by Li et al. are not SARMS as defined in the detailed description and claims of the instant application. Nor are the selective androgen receptor modulators of Edwards et al. or Hamann et al. since they do not exhibit antagonist activity in hormone-dependent tumors while exhibiting no activity or agonist activity against other, nontumor tissues containing the androgen receptor. Instead, the compounds disclosed by Edwards et al. and Hamann et al. are demonstrated to have partial agonist activity in an engineered reporter assay in a CV1 (green monkey kidney cells) assay in which both the AR and reporter constructs are transfected into the cell. No data are presented or discussed in either of these references with respect to the effects of these compounds as antagonists that inhibit growth of hormone-dependent tumors.

Accordingly, the secondary references of Zhi et al. and Li et al. cited in this combination of prior art do not remedy the Examiner's acknowledged deficiency in the teachings of Thorpe et al., namely no mention of selective androgen receptor modulators. Thus, the cited combination of prior art fails to provide the requisite motivation or suggestion to arrive at the instant invention; the combination of references

Attorney Docket No.: **BMS-0015**
Inventors: **Salvati et al.**
Serial No.: **09/885,827**
Filing Date: **June 20, 2001**
Page 22

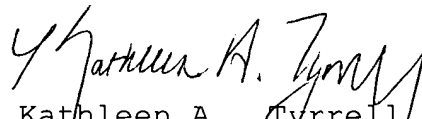
fails to provide any reasonable expectation of success with respect to the instant invention; and finally, the cited combination fails to teach or suggest all the limitations of the instant claimed invention. Thus, the basic requirements of a *prima facie* case of obviousness, as set forth in MPEP 2143 are not met by this combination of references.

Therefore, withdrawal of this rejection under 35 U.S.C. 103 is respectfully requested.

VII. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



Kathleen A. Tyrrell
Registration No. 38,350

Date: **June 16, 2003**

LICATA & TYRRELL P.C.
66 East Main Street
Marlton, New Jersey 08053
Tel : 856-810-1515